REMARKS

Applicants and their Attorney thank the Examiner for the courtesy of the November 6 and November 8, 2006 telephonic interviews during which the foregoing claim amendments and the outstanding rejections were discussed.

Claims 1-14, 70, and 71 were pending in the application. Claims 2-4, 6, 9-11 and 13 have been cancelled, without prejudice. Claims 1, 5, 8, and 12 have been amended. Thus, upon entry of the present amendment, claims 1, 5, 7-8, 12, 14, and 70-71 will remain pending in the application.

Support for the amendments to the claims may be found throughout the specification and the claims as originally filed. In particular, support for the amendments to claims 1 and 8 can be found, at least at, page 7, lines 27-29; page 10, lines 3-5; page 14, lines 19-24; page 68, lines 3-4; and page 70, lines 31-38 of the specification. Support for the amendments to claims 5 and 12 can be found, at least in, Tables 1-2B and at page 5, lines 3-5 and at page 10, lines 3-5 of the specification.

Any amendments to and/or cancellation of the claims was done solely for the purpose of expediting prosecution of the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed in this or a separate application(s).

No additional search is required and no new issues have been raised by the amendments made herein. Furthermore, in view of the amendments and arguments set forth herein, the number of issues for appeal has been reduced. Therefore, the claim amendments made herein are permissible under 37 C.F.R. §1.116 as reducing the number of issues for appeal, and Applicants respectfully request that the present Amendment be entered.

Advisory Action

In the Advisory Action dated October 18, 2006, the Examiner has indicated that the Amendment and Response filed on October 2, 2006 has not been entered because the amendments to claims 5 and 12 would raise new issues under 35 U.S.C. §112, first and/or second paragraph. According to the Examiner, "SEQ ID NO:16, however, is the polynucleotide sequence of a complementary DNA (cDNA) molecule; and no such mRNA transcript would exist in the sample."

Responsive to the Examiner's comments, Applicants present herein new amendments to claims 5 and 12, thereby rendering the foregoing issues raised by the Examiner moot. Specifically, claims 5 and 12 have been amended to specify that the amount of "an mRNA molecule comprising the corresponding RNA sequence of the polynucleotide sequence of SEQ ID NO:16" is detected. Applicants respectfully note that the claims have been amended based upon the Examiner's suggestions (see page 12 of the Final Office Action), however, Applicants have slightly modified the suggested claim language in order to be more scientifically accurate.

As the Examiner knows, "[t]ranscription involves synthesis of an RNA chain representing one strand of a DNA duplex," *i.e.*, the RNA transcript is *identical in sequence (except for the substitution of U for T)* to the exonic sequences of the DNA coding strand. This concept is graphically depicted in Figure 14.1 of Genes V, in which the green RNA transcript is identical to the green DNA coding strand (see Figure 14.1 of Genes V, Edition of 1994, see page 377 in Appendix A submitted herewith).

Reverse transcription makes it possible to synthesize a duplex DNA from any mRNA molecule (see Figure 21.5, of Genes V, see page 641 in Appendix A). First, a primer is annealed to the poly(dA) tail of the mRNA. The enzyme, reverse transcriptase, engages in the usual 5'-3' elongation, adding deoxynucleotide one at a time, as directed by complementary base pairing with the mRNA template (described in detail at page 641). A reaction occurs at the end of the mRNA, in which the enzyme causes the reverse transcript to 'loop back' on itself, by using the last few bases of the reverse transcript as a template for synthesis of a complement. The product of the reaction is a hybrid molecule, consisting of a template RNA strand base-paired with the complementary DNA strand. The original mRNA is then degraded by treatment with alkali and **the product is a single stranded DNA that is complementary to the mRNA; it is called cDNA** (see page 642 of Genes V). The hairpin at the 3' end of the cDNA provides a natural primer for the next step, the use of *E. coli* DNA polymerase I to convert the single-stranded

cDNA into a duplex DNA. In this reaction, the enzyme uses the cDNA as template **for synthesis of a sequence identical with the original mRNA except for the substitution of T in the DNA for U in the original RNA** (page 642).

This is called a **cDNA clone**. (From the terminology, a somewhat looser use of the term 'cDNA' has emerged, being taken to describe the duplex insert and not just the original single-stranded reverse transcript) (page 642).

For the Examiner's convenience, Applicants provide below a simplified representation of the processes described above.

5'-ATGCGCCAT-3' [DNA coding strand] ⎫ DNA
3'-TACGCGGTA-5' [DNA Non-coding strand/template strand] ⎭

↓ Transcription

5'-AUGCGCCAU-3' [mRNA sequence is complementary to DNA non-coding strand and identical to the DNA coding strand] ⎫ mRNA

↓ Reverse Transcription

5'-ATGCGCCAT -3' [Coding strand, *e.g.*, SEQ ID NO:16] ⎫ cDNA
3'-TACGCGGTA-5' [Non-coding strand] ⎭

As evidenced by all of the foregoing, the cDNA coding strand, *e.g.*, SEQ ID NO:16, is identical to the mRNA sequence (except for the substitution of U with T); it is not the complement of the mRNA sequence. Thus, Applicants respectfully request that the amended claim language "an mRNA molecule comprising the corresponding RNA sequence of the polynucleotide sequence of SEQ ID NO:16" be considered and entered by the Examiner.

The foregoing amendments were made solely in the interest of expediting prosecution and allowance of the present application and do not in any way reflect an acquiescence to any of the Examiner's rejections.

Objections to the Oath

The Examiner has objected to the oath/declaration as being defective for having non-initialed and/or non-dated alterations.

Applicants are in the process of contacting Edwin Clark to obtain a new oath/declaration in compliance with 37 C.F.R. §1.67(a). Applicants will submit the new oath/declaration as soon as it is available and certainly prior to the issuance of the present application.

Elections/Restrictions

The Examiner is of the opinion that "claims 1, 5-8, 11-14, 70 and 71 are directed to an invention(s) that is (are) independent or distinct from the invention originally claimed" (page 3 of the Office Action). According to the Examiner, the elected invention was drawn to

> a process for determining whether an agent can be used to reduce the growth of a tumor, said process comprising obtaining a sample of tumor cells and determining whether the tumor cells express one or more sensitivity markers, wherein said 'agent' is a combination of a taxane compound and a platinum compound.

The Examiner objects to the claims on the grounds that they are directed to any agent selected from the group consisting of TAXOL, TAXOL mimics, TAXOL analogs, TAXOL derivatives, cisplatin, cisplatin mimics, cisplatin analogs, and cisplatin derivatives.

Applicants acknowledge the election of the species of SEQ ID NO:16 and, further, the species election of a combination of agents consisting of a taxane compound and a platinum compound. Responsive to the Examiner's comments, Applicants have cancelled claims 2-3 and 9-10, without prejudice, as being directed to a non-elected invention. In the interest of expediting prosecution, and in no way acquiescing to the Examiner's objection, Applicants have also cancelled claims 4 and 11, without prejudice. Moreover, Applicants have amended claims 1 and 8 to specify that the claimed agent is "paclitaxel and cisplatin."

It is Applicants' understanding that upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species that are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. §1.141 *et seq*. Claims 1, 5-8, 12-14, and 70-71 read on the elected species of a combination of agents consisting of a taxane compound and a platinum compound. Claims 1, 5, 6, 8, 12, 13, 70, and 71 read on the elected species of SEQ ID NO:16.

Objection to the Specification

The Examiner has objected to the specification for containing embedded hyperlinks and/or other form of browser-executable code and for the use of improperly demarcated trademarks.

Responsive to the Examiner's objection, Applicants have submitted a Substitute Specification in which such hyperlinks have been removed and the improperly demarcated trademarks have been corrected. Accordingly, Applicants respectfully request reconsideration and withdrawal of this objection.

Rejection of Claims 1, 4-8, 11-14, 70, and 71 Under 35 USC § 112, First Paragraph

The Examiner has rejected claims 1, 4-8, 11-14, 70, and 71 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner's grounds for rejection are two-fold and Applicants will address each issue in turn.

Firstly, the Examiner asserts that "the claims are directed to a variety of structurally and/or functionally distinct compounds, which are not necessarily 'taxanes' or 'platinum compounds,' per se" (see page 10 of the Office Action). The Examiner concludes that "...the specification would not permit the skilled artisan [to] immediately envision, recognize or distinguish at least a substantial number of these compounds, so as to recognize that Applicant did in fact have possession of the claimed invention at the time the application was filed."

Applicants respectfully traverse the aforementioned rejection and respectfully submit that there is sufficient written description in Applicants' specification regarding the claimed methods, and that "the description clearly allow[s] persons of ordinary skill in the art to recognize that [Applicants] invented what is claimed" (see M.P.E.P. §2163.02). In particular, the present specification teaches that TAXOL and cisplatin are chemical compounds within the family of taxane and platinum compounds, respectively, which are art-recognized as families of *related* compounds (page 66, lines 4-5; and page 69, line 34 through page 70, line 1 of the specification) and Applicants further describe identifying characteristics of the members of these families, including the structure of analogs and derivatives that are structurally or functionally similar to TAXOL or cisplatin (see page 66, line 3 through page 70, line 24 of the specification).

However, in the interest of expediting prosecution, and in no way acquiescing to the validity of the Examiner's rejection, Applicants have amended claims 1 and 8 such that they are now directed to "***paclitaxel and cisplatin***," thereby rendering the foregoing rejection moot.

Secondly, the Examiner is of the opinion that the specification does not sufficiently describe the chemical structure of SEQ ID NO:16 (see pages 11-14 of the Office Action), namely, the specification does not sufficiently describe the genomic DNA molecule corresponding to SEQ ID NO:16 (11-12 of the Office Action) or the structure of the protein encoded by SEQ ID NO:16 (see page 12 and 14 of the Office Action).

Applicants respectfully traverse the rejection for the reasons of record. In addition, Applicants wish to make the following remarks of record. A description of the corresponding genomic sequence is <u>not</u> required to practice the claimed invention. Based on the nucleotide sequence of a marker of the invention, such as, for example, the marker of SEQ ID NO:16 (depicted in Tables 2A-2B as "jlhbab412e01"), one of skill in the art would readily be able to design probes or primers suitable for detecting the expression of this marker (as described at, for example, page 15, lines 30-35 and page 17, lines 12-19 of the specification). Moreover, it is well known in the art that the amino acid sequence corresponding to a nucleic acid sequence may be determined by identifying the open reading frame or translating the sequence in all three reading frames using well known programs designed to identify open reading frames and/or translate the nucleotide sequence in all frames. Therefore, based on the disclosure of the nucleotide sequences of the markers of the invention and the teaching in the specification that these sequences represent expressed products, one of skill in the art would conclude that Applicants were in possession of the corresponding protein sequence at the time of filing.

However, Applicants respectfully submit that in the interest of expediting prosecution, and in no way acquiescing to the validity of the Examiner's rejection, Applicants have cancelled claims 6 and 13, thereby rendering the foregoing rejection moot.

In view of the foregoing, Applicants respectfully request that the aforementioned rejection be reconsidered and withdrawn.

Rejection of Claims 1, 4-8, 11-14, 70, and 71 Under 35 USC § 112, First Paragraph

The Examiner has rejected claims 1, 4-8, 11-14, 70, and 71 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. ***The Examiner admits that "the specification teaches a correlation between the presence of one or more adequately***

described markers in ovarian cancer cells and their sensitivity or lack thereof to a combination of Taxol™ (paclitaxel) and cisplatin" (emphasis added). However, the Examiner is of the opinion that "[t]he combination of Taxol™ and cisplatin is not representative of the whole of the genus of agents to which the claims are directed" (page 16 of the Office Action).

Applicants traverse the foregoing rejection for the reasons of record. It is Applicants' position that the amount of direction and guidance disclosed in the specification is commensurate with the scope of the claims and sufficient to enable the skilled artisan to make and use the claimed methods using only routine experimentation.

However, in the interest of expediting prosecution, and in no way acquiescing to the validity of the Examiner's rejection, Applicants have amended claims 1 and 8 such that they are now directed to ***"paclitaxel and cisplatin."*** The Examiner has admitted in the present Office Action that the specification is enabling for such methods (see above). Thus, Applicants respectfully submit that the foregoing rejection has been rendered moot and request that the Examiner reconsider and withdraw this rejection.

The Examiner has also questioned why "...the absence or underexpression of the one or more markers and the tumor cells' insensitivity to an agent are inversely correlated, whereas it is merely the presence of the marker, rather than its overexpression that allegedly positively correlates with the tumor cells' sensitivity to the agent." The Examiner further asserts that "[t]he specification fails to teach whether it is the mere presence of such markers, or their relative levels of expression that correlate with tumor cells' sensitivities to agents" (page 20 of the Office Action).

Applicants respectfully traverse this rejection. With respect to the ***absence versus the presence of a marker***, the Applicants teach, at page 70, lines 31-38 of the specification, that

> [i]f the gene is expressed, and the marker of the invention to which the gene corresponds is a sensitivity marker, then the therapeutic agent will be effective against the cancer. Accordingly, if a sensitivity marker is not expressed, then the therapeutic agent will not be effective against the cancer. If a resistance marker of the invention is expressed, then the therapeutic agent will not be effective against the cancer. Accordingly, if the resistance marker is not expressed, then the therapeutic agent will be effective against the cancer.

With respect to the ***relative level of expression of a marker***, Applicants teach, at page 71, lines 3-13 of the specification, that

> [b]y examining the expression of one or more of the identified markers in a sample of cancer cells taken from a patient during the course of therapeutic treatment, it is also possible to determine whether the therapeutic agent is continuing to work or whether the cancer has become resistant (refractory) to the treatment protocol. For example, a cancer patient receiving a treatment of TAXOL would have cancer cells removed and monitored for the expression of a marker. If the expression level of a sensitivity marker remains substantially the same, the treatment with TAXOL would continue. However, a significant decrease in sensitivity marker expression or increased expression of a resistance marker, would suggest that the cancer may have become resistant to TAXOL and another chemotherapy protocol should be initiated to treat the patient.

Furthermore, the specification provides a ***description of the standard to which such comparisons of the levels of expression are to be made.*** For example, at page 6 lines 13-21 of the specification, expression levels are defined a follows:

> [e]xpression of a marker in a patient is 'significantly' higher or lower than the normal level of expression of a marker if the level of expression of the marker is greater or less, respectively, than the normal level by an amount greater than the standard error of the assay employed to assess expression, and preferably at least twice, and more preferably three, four, five or ten times that amount. Alternately, expression of the marker in the patient can be considered 'significantly' higher or lower than the normal level of expression if the level of expression is at least about two, and preferably at least about three, four, or five times, higher or lower, respectively, than the normal level of expression of the marker.

Applicants also teach the use of normalization by comparing the expression of a marker of the instant invention "to the expression of a gene that is not a sensitivity or resistance gene, *e.g.*, a housekeeping genes that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene" (page 14, lines 34-37 of the specification).

In an effort to expedite prosecution and in no way conceding the validity of the Examiner's rejection, Applicants have amended claim 8 to specify "one or more of the sensitivity markers in Tables 1-6 is not expressed by the ovarian tumor cells," thereby rendering the foregoing rejection moot.

Based on the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §112, first paragraph.

New Grounds of Rejection

Rejection of Claims 1, 4-8, 11-14, 70, and 71 Under 35 USC § 112, Second Paragraph

The Examiner has rejected claims 1, 4-8, 11-14, 70, and 71 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner is of the opinion that "[t]he claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product."

In an effort to expedite prosecution and in no way conceding the validity of the Examiner's rejection, Applicants have amended claims 1 and 8 to recite "paclitaxel," thereby rendering the foregoing rejection moot.

The Examiner is further of the opinion that claims 5 and 12 are indefinite because "[t]he polynucleotide sequence of SEQ ID NO:16 is not the sequence of an RNA molecule; and the term 'SEQ ID NO:16 mRNA' is not defined in the specification."

Without acquiescing to this rejection and solely in an effort to further prosecution, Applicants have amended claims 5 and 12 to specify that the amount of "an mRNA molecule comprising the complement of the polynucleotide sequence of SEQ ID NO:16" is detected, as suggested by the Examiner (see page 12 of the Final Office Action). In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

CONCLUSION

In view of the foregoing, entry of the amendments and remarks presented, favorable reconsideration and withdrawal of the rejections, and allowance of this application with the pending claims are respectfully requested. If a telephone conversation with the Applicants' attorney would expedite prosecution of the above-identified application, the Examiner is invited to call the undersigned at (617) 227-7400.

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Respectfully submitted,

By _____

Maria Laccotripe Zacharakis, Ph.D., J.D.
Registration No.: 56,266
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicants